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PREPARATION AND EVALUATION OF TAPENTADOL MOUTH DISSOLVING TABLETS

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Abstract:
Mouth dissolving tablets are solid dosage forms containing tapentadol as active pharmaceutical ingredient which has analgesic effect, and has superdistegrants like croscarmellose sodium and starch glycolate which disintegrates fast usually less than 60 seconds without the need of water when placed on the tongue. To prepare and evaluate tapentadol mouth dissolving tablet by using direct compression method and to determine the effect of formulation process and the excipients. Tapentadol MDT were formulated by using ingredients and superdisintegrants like sodium starch glycolate and cross carmellose.The resulting tablets were evaluated using parameters such as: hardness, friability, disintegration time in vitro, modified disintegration time, disintegration time in the oral cavity, wetting time, water absorption ratio, drug content determination, weight uniformity, and dissolution. The results showed that tapentadol mouth dissolving Tablets fulfilled the requirements for all parameters except for F1 formula that did not produce physical shape intact tablet. MDT s used higher amount of crosscarmellose showed faster disintegration time. FTIR studies and calibration curve show there is interaction between drug and excipients tablet hardness were also higher. In vitro drug release of all formulation MDTS showed fast drug release with in few sec. The study reveals that formulations prepared by direct compression F3 exhibits highest dissolution using cross carmallose sodium showed faster drug release 90.15% over the period of 50min while disintegration time of the tablet was showed 50sec in comparison to other formulations of tapentadol.

Keywords: *sodium starch glycolate,crosscarmellose sodium, disintegration tapentadol mouth dissolving tablets.*

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INTRODUCTION:

For administration of drugs, oral route is considered the most widely used route. In this method the main limitation of commonly used oral drug delivery such as tablets and capsules is swallowing difficulty (dysphasia) mostly in case of pediatric and geriatric patients feel most incompliance to take the tablets and capsules. To make the patients convenient for the administration of these dosage forms plays a vital in design and formulation of dosage forms[1].

For mouth dissolving tablet formulation the main criteria is to eliminate the bitterness of the tablet by adding sweetening agent or by sugar coating on the tablets.To overcome this problem and to make the oral route more convenient for patients a new drug delivery method is evolved known as mouth dissolving drug delivery system, These MDTs should dissolve or disintegrate in the mouth within few seconds without the need of water, chewing with the help of saliva present in the mouth.

To increase the tablet disintegration, super-disintegrants are added in it, which are very helpful to increase the bioavailability of tablet and to increase the disintegration property of tablet in saliva. Disintegrants are mainly added in the tablets by three methods. These methods are extra- granular, intra-granular and partially extra- granular and intra-granular method. Time for MDT disintegration is normally assumed to be less than 1 min.

The patients can feel the normal disintegration time of MDT from 5-30sec. MDT's are mainly prepared by various methods like direct compression, wet granulation, solid dispersion and tablet molding etc. Direct compression method is the most widely used and easiest or cost effective method for MDT as compared to other methods.

DEFINITION:

Mouth dissolving tablet (MDT) It is a tablet that disintegrates and dissolves rapidly in the saliva, within a few seconds without the need of drinking water or chewing. A mouth dissolving tablet usually dissolves in the oral cavity within 15 s to 3min. Most of the MDTs include certain super disintegrates and taste masking agents.

MDT's are mainly used in some serious conditions like:

1. Motion sickness
2. Parkinsonism
3. Pediatric and geriatric patients
4. Unconsciousness
5. Mentally disabled patients
6. Absence of water[2]

Ideal characteristics of MDT:

1. A MDT should be dissolve or disintegrate in the mouth within few seconds.
2. It should not require any liquid or water to show its action.
3. It should not leave any residue in the mouth after the administration of the tablet.
4. It should be cost effective.
5. It should be less effective by environmental conditions like humidity, temperature etc.

MDT advantages:

1. Easy for administration to patients which cannot swallow he tablets like pediatric and geriatric, unconscious and mentally disabled patients**.**
2. Does not require water to take the tablet during travelling.
3. Quick disintegration and dissolution of drug tablet to produce rapid action.
4. Bioavailability of drug can be increased by avoiding the passage of the drug from pharynx and esophagus.
5. It has good mouth feel property that helps to take the medicine easily than the bitter pills in pediatric patients.
6. There is no risk of suffocation and chocking during MDT uptake.
7. It is helpful in some cases like motion sickness, during coughing etc.
8. These MDT's are stable for longer duration of time, till it is consumed [3].

Disadvantage of mouth dissolving tablets:

1. Fast dissolving tablet is hygroscopic in nature so must be keep in dry place.
2. Some time it possesses mouth feeling.
3. MDT requires special packaging for properly stabilization & safety of stable product.[4]

Important Criteria for Excipients Used in The Formulation of MDTS:[5]

1. It must be able to disintegrate quickly.
2. Their individual properties should not affect the MDTs.
3. It should not have any interactions with drug and other excipients.
4. It should not interfere in the efficacy and organoleptic properties of the product.
5. When selecting binder a (single or combination of binders) care must be taken in the final integrity and stability of the product.
6. The melting points of excipients used will be in the range of 30-350C.
7. The binders may be in liquid, semi liquid, solid

or polymeric mixtures.
8. (Ex: Polyethylene glycol, coca butter, hydrogenated vegetable oils)

Salient features of mouth dissolving tablets:
1. Ease of administration to patients who refuse to swallow a tablet, such as pediatric and geriatric patients and, psychiatric patients.
2. Convenience of administration and accurate dosing as compared to liquids.
3. Rapid dissolution of drug and absorption which may produce rapid, onset of action.
4. Some drugs are absorbed from the pharynx and esophagus as the saliva passes down into the stomach, in such cases bioavailability of drugs is increased.
5. Ability to provide advantages of liquid medication in form of solid preparation.
6. Pre-gastric absorption can result in improved bioavailability and as a result of reduced dosage, improved clinical performance through a reduction of unwanted effects.

Limitations of mouth dissolving tablets:
1. The tablets usually have insufficient mechanical strength. Hence, careful handling is required.
2. The tablets may leave unpleasant taste and/or grittiness in mouth if not formulated Properly
3. Drugs which are having relatively lager doses are difficult to formulate in form of fast disintegrating tablet example like ciprofloxacin.
4. Patients who concurrently taking medicine like anticholinergics may not be the best candidates for fast disintegrating tablets and the patients suffers from Sjogren's syndrome or dryness of mouth due to decreases saliva production may not be good candidate for such type of formulation.

Significance of Odts [6,7] :
ODTs offer dual advantages of solid dosage forms and liquid dosage forms along with special
Features which include:

Accurate dosing:
Being unit solid dosage forms, provide luxury of accurate dosing, easy portability and manufacturing, good physical and chemical stability and an ideal alternative for pediatric and geriatric patients.

Enhanced bioavailability:
Bioavailability of drugs is enhanced due to absorption from mouth, pharynx and oesophagus.

Rapid action:
Fast onset of therapeutic action as tablet gets disintegrated rapidly along with quick dissolution and absorption in oral cavity.

Patient compliance:
No need of water to swallow the dosage form. Hence, it is convenient for patients who are traveling and do not have immediate access to water.

Ease of administration:
Convenient to administer specially for geriatric, paediatric, mentally disabled and bed ridden patients who have difficulty in swallowing.

Obstruction free:
No risk of suffocation in airways due to physical obstruction when swallowed, thus providing improved safety and compliance.

Enhanced palatability:
Good mouth feels, especially for pediatric patients as taste masking technique is used to avoid the bitter taste of drug.

Simple packaging:
No specific packaging required. It can be packaged in push through blisters.

Business Avenue:
Provide new business opportunities in the form of product differentiation, line extension, uniqueness and life cycle management.

Cost effective:
Conventional processing and packaging equipments allow the manufacturing of tablets at low cost.

Formulation of MDT's:
Drug:
The ultimate characteristics of a drug for dissolution in the mouth and pre gastric absorption from MDTs include:
* Free from bitter taste
* Dose lower than 20 mg
* Small to Moderate molecular weight
* Good solubility in saliva
* Ability to permeate through oral mucosal tissue [7].

Bulking materials:
Bulking materials are significant in the formulation of fast-melting tablets. The material contributes functions of a diluent, filler and cost reducer. Bulking agents improve the textural characteristics that in turn enhance the disintegration in the mouth, besides; adding bulk also reduces the concentration of the active in the composition. The recommended bulking agents for this delivery system should be more sugar-

based such as mannitol, polydextrose, lactitol, DCL (direct compressible lactose) and starch hydrolystate for higher aqueous solubility and good sensory perception. Mannitol in particular has high aqueous solubility and good sensory perception. Bulking agents are added in the range of 10 percent to about 90 percent by weight of the final composition [8].

Emulsifying agents:
Emulsifying agents are important excipients for formulating fast-melting tablets they aid in rapid disintegration and drug release without chewing, swallowing or drinking water. In addition, incorporating emulsifying agents is useful in stabilizing the immiscible blends and enhancing bioavailability. A wide range of emulsifiers is recommended for fast-tablet formulation, including alkyl sulfates, propylene glycol esters, lecithin, sucrose esters and others. These agents can be incorporated in the range of 0.05 percent to about 15 percent by weight of the final composition [9].

Lubricants:
Lubricants, though not essential excipients, can further assist in making these tablets more palatable after they disintegrate in the mouth. Lubricants remove grittiness and assist in the drug transport mechanism from the mouth down into the stomach [10].

Flavours and sweeteners:
Flavours and taste-masking agents make the products more palatable and pleasing for patients. The addition of these ingredients assists in overcoming bitterness and undesirable tastes of some active ingredients. Both natural and synthetic flavours can be used to improve the organoleptic characteristic of fast-melting tablets. Formulators can choose from a wide range of sweeteners including sugar, dextrose and fructose, as well as non-nutritive sweeteners such as aspartame, sodium saccharin, sugar alcohols and sucralose. The addition of sweeteners contributes a pleasant taste as well as bulk to the composition [10].

Superdisintegrants:
A disintegrant is an excipient, which is added to a tablet or capsule blend to aid in the breakup of the compacted mass when it is put into a fluid environment [10].
Super disintegrants like:
Sodium starch glycolate
crosscarmellose sodium,
crosscopovidone

Advantages:
1. Effective in lower concentrations.
2. Less effect on compressibility and flowability.

MATERIALS AND METHODS:

Materials:
Tapentadol procured as a gift sample from MSN Organics Pvt Ltd. Bibinagar, Telangana, India, Sodium starch glycolate, lactose, Croscarmellose sodium purchased from Merck Specialities Pvt Ltd, Mumbai, India, Mannitol, Magnesium stearate, Talc purchased from Qualikem Pvt Ltd, India and all reagents are used in the laboratory are laboratory grades.

Methods:
The Tapentadol along with Polymers formulated in three different ratios into mouth dissolving tablet by direct compression method.

TABLE-1 FORMULATION CHART

Sl.No.	Ingredients	F1	F2	F3
1	Tapentadol	3 mg	3mg	3mg
2	Sodium starch glycolate	5mg	5mg	5mg
3	Croscarmellose sodium	20mg	30mg	40mg
4	lactose	22mg	22mg	22mg
5	Mannitol	45mg	35mg	25mg
6	Talc	3mg	3mg	3mg
7	Magnesium Stearate	2mg	2mg	2mg
8	TOTAL	100mg	100mg	100mg

Preparation and evaluation of mouth dissolving tablets:

Methodology

The Mouth dissolving tablets of Tapentadol were prepared by direct compression method. USING different superdisintegrants are used namely

- Croscarmellose sodium
- Sodium starch glycolate
- Three formulations were prepared using different superdisintegrants in a concentration ranging from 2% to 10% .An accurately weighed quantity of drug, superdisintegrants are taken in a glass mortar and ground well, the other excipients like mannitol, sodium starch glycolate,lactose, magnesium stearate and talc are added in an order and mixed well to ensure thorough mixing of all ingredients.
- The total powder blend is weighed individually for thirty tablets for each formulation, as per the calculations derived from the drug content of the powder blend. Then the individually weighed powders are compressed in the tablet compressing machine.

RESULTS AND DISCUSSION:

Calibration curve values:

The absorbance was measured in a UV spectrophotometer at 228nm against 7.4 pH buffer**.**

TABLE 2.CALIBRATION CURVE VALUES

S.No	Conc µg/ml	Absorbance
1	0	0
2	2.0	0.061
3	4.0	0.119
4	6.0	0.179
5	8.0	0.240
6	1.0	0.310

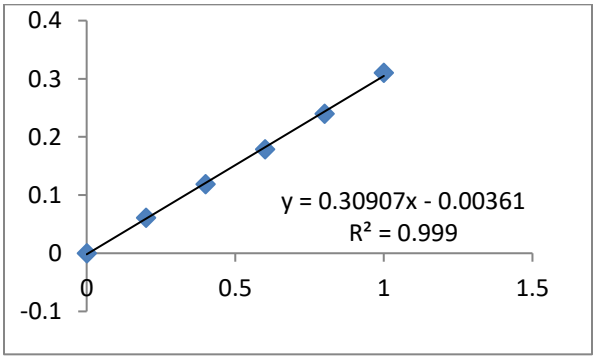

FIGURE 1. STANDARD GRAPH OF TAPENTADOL IN 0.1N HCL

Compatibility studies:

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Compatibility studies by FTIR studies:

The FTIR studies were conducted for completed physical mixture and drug substance. The completed physical mixture was evaluated against drug substance and the graphs of the same were shown in figure 01 - 02.

After completion of the study the IR spectrums were generated and spectrums of both active substance alone and physical mixture revealed that

the bands observed in the active substance were appeared in the physical mixture. This means that confirming the purity of active substance with standard respectively and interpretation data were given in table 06.

FTIR studies: The FTIR spectra of the pure drug were recorded in between 4000 to 400. Characteristics peak and chemical group present in IR spectrum of tapentadol were showed.

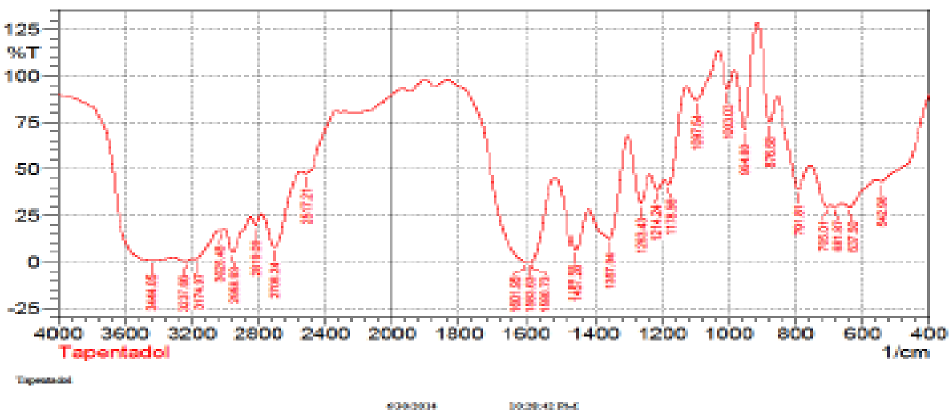

FIGURE 2. FTIR OF TAPENTADOL

Drug-excipient compatibility studies:
ompatibility studies by FTIR studies:
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After completion of the study the IR spectrums were generated and spectrums of both active substance alone and physical mixture revealed that the bands observed in the active substance were appeared in the physical mixture. This means that confirming the purity of active substance with standard respectively and interpretation data were give. These studies were performed in order to confirm the drug-excipient interaction.

These studies mainly include FTIR Spectroscopy. FTIR spectra of pure drugs and formulated MDT containing Tapentadol were recorded on FTIR Spectrophotometer. The scanning range was from

4000 to 600 cm^{-1} and the resolution was 1 cm^{-1}. The scans were evaluated for presence of principal peaks of drug, shifting and masking of drug peaks, and appearance of new peaks due to excipient interaction. This spectral analysis was employed to check the compatibility of drugs with the excipients used

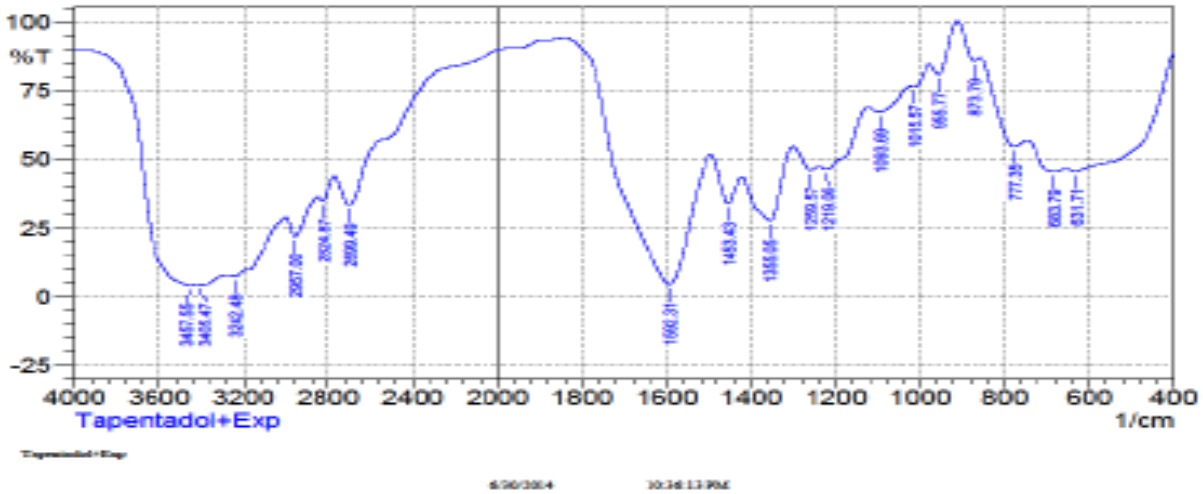

FIGURE 3. FTIR of Tapentadol and Excipients

Pre-Compression Results Of Tablets:-Table No: 3

Sl.No.	Pre-compression Parameter	F1	F2	F3
1	Angle of repose (°)	25.10	25.43	25.41
2	Bulk density (gm/cm^3)	0.53	0.54	0.54
3	Tapped density (gm/cm^3)	0.59	0.60	0.58
4	Carr's index	9.43	9.40	10.01
5	Hausner's ratio	1.11	1.10	1.07

Post-Compression Studies Of Tablet:-Table No:4

S. No.	Post-compression parameter	F1	F2	F3
1	Hardness (kg/cm^2)	3.3±0.5	3.2±0.5	3.5±0.5
2	% Weight variation	100±1.08	101±1.1	100±1.05
3	Friability (%)	0.9±0.11	0.1±0.2	0.5±0.1
4	Drug content (%)	99.5±0.5	98.7±.52	101±0.7
5	Disintegrating time (sec)	40±5	35±5	32±5

Wetting Time And Water Absorption: Table No:5

FORMULATION CODE	Wetting Time in sec
F1	13.43±4
F2	12.52±5
F3	12.44±9

***In Vitro* Dissolution Profile Of Formulation: - Table No:6**

The drug release rate from tablets was studied using the USP type II dissolution test apparatus. The dissolution medium was 500 ml of pH 6.8 phosphate buffer at 50 rpm at a temperature of 37±0.5 ˚C. Samples of 5 ml were collected at different time intervals up to 45 min and has analyzed after appropriate dilution by using UV spectrophotometer at 275 nm.

Time(min)	F3	F2	F1
0	0	0	0
5	14.36	10.14	7.05
10	25.26	19.55	13.05
15	39	30.11	25.05
20	53.01	45.03	35.03
25	66.24	55.02	42.01
30	68.74	61.94	50.44
35	85.32	71.02	55.94
40	86.74	75.11	62.55
45	88.54	81.01	70.22
50	90.15	85.05	79.01

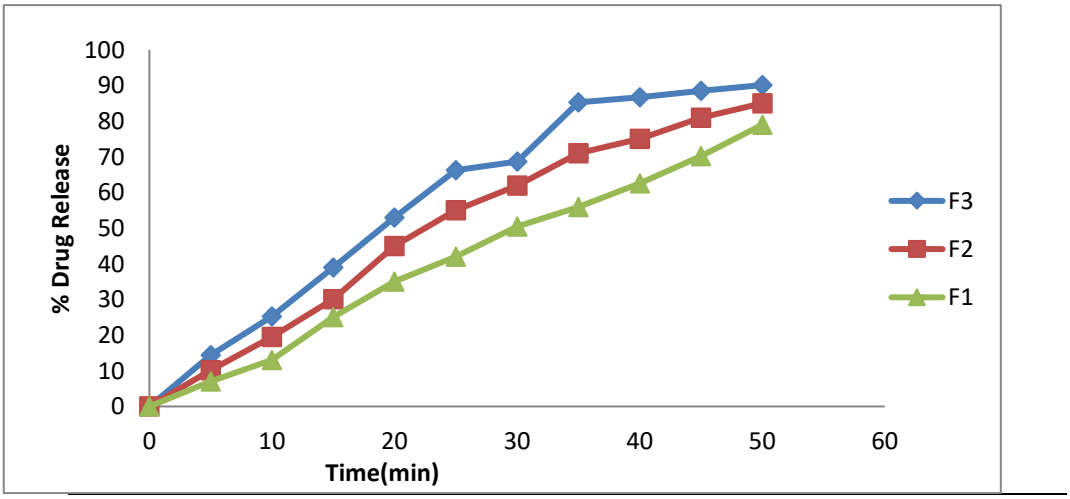

FIGURE 4. GRAPHS FOR DISSOLUTION PROFILE OF FORMULATION

Among all the formulations F3 formulation containing drug and CROSS CARMELLOSE showed good result that is 88.01 in 50 minutes, at the concentration of 80 mg. Hence from all the formulations it is evident that F2 formulation is the better formulation.

DISSCUSSION:

The individually weighed powder blends of each formulation were compressed in to tablets in a single punch tablet compressing machine. Ten tablets for each formulation were obtained. The tablets were white in colour and round in shape. The contents for tablets of each formulation were given below.

Precompression parameters:

Precompression evaluations were done to ensure the flow properties of the powder blend .Good flow properties of the powder blend will yield the tablets of desired quality and ease the tableting process. So it was mandatory to assess the flowability of the blend before compression. The various precompression evaluations were as follow.

a) Angle of repose
b) Bulk density
c) Tapped density
d) Compressibility Index
e) Hausner's ratio

a. **Angle of repose:**
The angle of repose was used for the measurement of frictional force in a loose powder which in turn will influence the flow properties of the powder blend. The angle repose of all the formulations ranges from 25.10 to 25.41. the results, that the powder blends of all formulations posses' good flow properties.

b. **Bulk density:**
The bulk density was determined to assess the free flowing property of the powder blend. The bulk density of all formulations ranges from 0.53 to 0.54.. The results indicate that the powder blends of all formulations were having good flow properties.

c. **Tapped density:**
The tapped densities of all formulations were determined to analyse the powder blends for their free flowing property. The tapped density of all the formulations ranges from0.59 to 0.58. From the results it shows that the powder blend of all formulations posses good flow properties.

d. **Carr's Index:**
The compressibility index was the simplest method to measure the free flowing of powder blends of all formulations. The ease with which a material was induced to flow was given by compressibility index. The compressibility index of all the formulations ranges from9.43 to 10.1.The results indicate that the powder blend of all formulations possess good flow properties.

e. **Hausner's ratio:**
The Hausner's ratio was an indirect index of ease of powder to flow. The Hausner's ratio for powder blends of all fifteen formulations ranges from 1.11 to 1.07. It was observed from the results that the powder blends of all formulations have good flow properties.

Hausner's ratio

< 1.25 – Good flow property

>1.25 – poor flow property

results of the precompression studies, that the powder blends of all the formulations posses good flow properties.

Post compression parameters:

The tablets obtained after compression were evaluated on various parameters to determine their quality.

f. **Hardness:**
The hardness for tablets determines the resistance of the tablets to abrasion or breakage under conditions of storage, transformation and handling before usage. The hardness for tablets of all the formulations ranges from 3.3±0.5 to 3.5±0.5 .The results indicate that the tablets of all formulations have uniform hardness.

g. **Drug content:**
The drug content of the tablets was estimated to ensure that all the tablets of a formulation contains the therapeutic dosage of the active ingredient meant for the particular dosage form. The drug contents for tablets of all the formulations ranges from 99.5±0.5 to 101±0.7. The results indicate that the contents for tablets of all formulations were uniform and contains therapeutic dose of the active ingredient.

h. **Weight variation test:**
The weight variation test was carried out to ensure that the tablets of each formulation were of uniform weight, which in turn will indicate the uniform distribution of contents of the powder blends of each formulations. The weight variation for tablets of all formulations was found to be within the range of 100±1.08 to 100±1.05 The results indicate that all tablets of each formulation were of uniform weight.

i. **Friability test:**
The friability test was carried out to ensure the mechanical strength of tablets to avoid the loss of the external surface of the tablets during the process of packing, handling, transit, and storage. Friability below 1% was an indication of good mechanical resistance. The results indicate that the friability for tablets of all formulations were below 1%and hence passes the test.

j. **Wetting time and Water absorption ratio:**
The wetting time and water absorption ratio indicates the capacity of the superdisintegrants to absorb water and completely wet the tablet at the earliest time possible, which were the significant characteristics of fast dissolving tablets. The minimum wetting time and maximum water absorption ratio will enable faster disintegration of the tablets, which were the prime important criteria for fast dissolving tablets. The wetting time for formulations, ranges from 13.43±4 to 12.44±9 seconds respectively .The results indicates that the wetting time and water absorption ratio of all tablets were within the limits.

k. **Disintegration time:**
The disintegration time was the time taken by the tablet to break down in to small particles, in the presence of aqueous medium. It varies with type and concentration of the superdisintegrants incorporated in the formulation. As the name implies disintegration time were the prime most criteria for fast dissolving tablets, which should be less than 30 secs to 3 minutes as per the standards. The disintegration time for formulations ranges from40±5 to 32±5.

l. **Dissolution studies:**
The dissolution studies were performed to evaluate the release profile of the drug, which relates the percentage of drug release from its dosage form with the function of time. The superdisintegrants were added to the solid dosage formulations to enhance the disintegration time and thereby enhancing the faster release of active drug from its dosage form, which ultimately results in enhanced rates of absorption and bioavailability of the drug. The desired quality of fast dissolving tablets was to have a maximum release of therapeutic dose at a very minimal time period. The maximum drug release at a time period of five minutes is noted for all the formulations. The drug release for tablets of all formulations ranges from 14.36 to 79.01 50 mins.
From the results obtained from the post compression studies of tablets of all formulations, the formulation 3 with concentration of 40% Crosscarmellose sodium was found to be the best formulation with a disintegration time of 30sec, wetting time of 12 secs and drug release of 95.15% which was the highest of all formulations.

CONCLUSIONS:

The formulation of tapentadol mouth dissolving is prepared by direct compression method by using different ratios of superdisintegrant cross carmollose sodium and sodium starch glycolate. Among all the formulations, the formulation F3 exhibits highest dissolution using cross carmollose sodium faster drug release 88.01%over the period of 50 min while disintegration time of the tablet was showed 12 sec. Therefore the prepared formulation of tapentadol mouth dissolving tablets containing cross carmollose sodium is best formulation and could be used for industrial application.

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